IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jim Wells et al.	Docket No.:	39750-0002DV1
Serial No.:	09/981,547	Group Art Unit:	1639
Filing Date:	October 17, 2001	Examiner:	Epperson, Jon D.

For: **METHODS FOR RAPIDLY IDENTIFYING SMALL ORGANIC MOLECULE LIGANDS FOR BINDING TO BIOLOGICAL TARGET MOLECULES**

Commissioner of Patents &Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF GARY SIUZDAK, Ph.D.

Sir:

I, GARY SIUZDAK, Ph.D. declare that:

1. I am currently the Senior Director at the Center for Mass Spectrometry and Associate Professor of Molecular Biology at The Scripps Research Institute. My field of expertise includes the use of mass spectrometry in biological applications. My degrees include a B.S. in Chemistry and a B. A. in Mathematics from Rhode Island College (1985) and a Ph.D. in Physical Chemistry from Dartmouth College (1990).

2. Among my many publications in the field of mass spectrometry include the book MASS SPECTROMETRY FOR BIOTECHNOLOGY, New York, Academic Press (1996). As I understand it, an Examiner in the Patent and Trademark Office has cited Chapter 6 (titled Specific Applications), pages 119-126, in the examination of a patent application. The claimed invention relates to a screening method where novel ligands are identified by subjecting a mixture of a target protein and a plurality of potential ligands that are each capable of forming a covalent bond with the protein to mass spectrometry analysis, and detecting the most abundant covalently bound protein-ligand conjugate that is formed, and identifying the ligand present in the conjugate.

3. As I understand it, the Examiner finds similarity between the claimed invention and the specific applications described in pages 119-126 of my book, particularly the analysis of the mechanism of catalytic antibodies and enzymes where mass spectrometry was used to study the covalently bound substrate-antibody/enzyme intermediates of the respective reactions. Because the cited portion ends with a statement that "[e]lectrospray ionization mass spectrometry has also demonstrated its potential...for observing covalent protein-bound intermediates in an antibody-catalyzed reaction," the Examiner appears to have concluded that this statement would have provided a person skilled in the art with motivation to use electrospray ionization mass spectrometry, or mass spectrometry in general, to identify novel ligands of proteins by detecting covalently bound ligand-protein conjugates in a similar manner.

4. I respectfully disagree with the Examiner that the cited statement would have motivated a person skilled in the art to identify a novel ligand by the mass spectrometry detection of a covalently bound protein-ligand conjugate in a mixture.

5. Studies of enzymatic mechanisms involve the detailed characterization of a single reaction where the participants, namely an enzyme and its substrate, are known. As a result, the important aspect of these studies is not determination of the identity of the binding partner of the enzyme (which is known) but to detect the non-covalent binding of the substrate to the enzyme, the formation of the covalent enzyme-substrate intermediate, and finally the dissociation of the product and the enzyme.

6. While electrospray ionization mass spectrometry is well suited to study enzymatic mechanisms where all of the participants are known, its use to analyze mixtures of unknown components is limited. Because heterogeneous compounds can produce complicated spectra that can be difficult or impossible to interpret, samples for electrospray ionization mass spectrometry usually have to be of very high purity. Another obstacle for the use of this technique is that heterogeneous mixtures tend to reduce the sensitivity of electrospray ionization mass spectrometry. Many of these obstacles are shared by other techniques of mass spectrometry.

7. Consequently, I do not believe that a person skilled in the art would have assumed that the mass spectrometry techniques to study enzymatic mechanisms would have been applicable to identify novel ligands by the mass spectrometry analysis of a mixture of unknown chemical entities, detecting a covalently bound protein-ligand conjugate from among the chemical entities present in the mixture, and determining the identity of the ligand present in the conjugate detected.

I further declare that all statements made herein of my own knowledge are true; and that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: February 15, 2005 By: _____
Gary Siuzdak, Ph.D.